FORMULATION, DEVELOPMENT AND EVALUATION OF MONTELUKAST SODIUM CHEWABLE TABLETS

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In

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By

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TAMIL NADU

MAY 2012

CERTIFICATES

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This is to certify that the dissertation entitled **"FORMULATION, DEVELOPMENT AND EVALUATION OF MONTELUKAST SODIUM CHEWABLE TABLETS"** is a bonafide and genuine research work carried out at the Department of Pharmaceutics, K.K College of pharmacy by **NARESH KUMAR GUPTA, B.Pharm.,** during the year 2011-2012 under the supervision of **Asst. Prof. Mrs. Pheeba Mary Philip M.Pharm.,** This dissertation is submitted for partial fulfillment of the requirements for the award of degree of Masters of Pharmacy (Pharmaceutics), by the Tamil Nadu Dr. M.G.R Medical University, Chennai-32.

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Place: CHENNAI *Naresh Kumar Gupta*

Date:

ABBREVATIONS

gm	- Gram
ml	- Milliliters
mm	- Millimeters
cm	- Centimeters
BD	- Bulk Density
TD	- Tapped Density
CI	- Carr's Index
HR	- Hausner's Ratio
Kp	- Kilo Pounds
^{o}C	- Centigrade
%RH	- Percentage Relative humidity
RPM	- Revolutions Per minute
HPLC	- High pressure liquid chromatography
% CDR	- Percentage Cumulative Drug Release
PO	- per os
CDER	-Centre for Drug Evaluation and Research
FDA	-Food and Drug Administration
EMEA	-European Medicine And Evaluation Agency

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INTRODUCTION

Oral solid dosage form[1,2]:

The oral route of drug administration is the most important method of administering drug for systemic effects. Except in certain case the parental route is not routinely used for self administration, e.g. insulin. The topical route of administration has only recently been employed to deliver drugs to the body for systemic effect. The parental route of administration is important in treating medical emergencies in which the subject is comatose or cannot swallow. Nevertheless it is probable that at least 90% of all drugs used to provide systemic effect are administered by oral route. When a new drug is discovered one of the first question a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by oral route. Drugs that are administered orally, solid oral dosage forms represent the preferred class of product. Tablet and capsules represent unit dosage forms in which usual dose of drug has been accurately placed.

Tablets and capsules represent unit dosage forms in which one usual dose of drug has been accurately placed. By comparison liquid forms such as syrups, suspensions, emulsions, solutions and elixirs are usually designated to contain one medication in 5 -30ml, such dosage measurements are typically error by a factor ranging from 20 -50%, when the drug is self administered by patient.

Tablets[3,4]:

In 1843, the first patent for a hand operated device used to form a tablet was granted. Tablets are defined as solid dosage forms each containing a single dose of one or more active ingredients, obtained by compressing uniform volumes of particles. They are intended for the oral administration, some are swallowed whole, some after being chewed. Some are dissolved or dispersed in aqueous phase before being administered and some are retained in the mouth, when the active ingredients are “liberated”.

Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use drug must be released from tablet that is dissolved in the fluids of mouth, stomach and intestine and then absorbed into systemic circulation by which it reaches its site of action.

The tablet is composed of the Active Pharmaceutical Ingredient (active drug) together with various excipients. These are biologically inert ingredients which either enhance the

therapeutic effect or are necessary to construct the tablet. The filler or diluents (e.g. Lactose or Sorbitol) are a bulking agent, providing a quantity of material which can accurately be formed into a tablet. Binders (e.g. methyl cellulose or gelatin) hold the ingredients together so that they can form a tablet. Lubricants (e.g. magnesium stearate or polyethylene glycol) are added to reduce the friction between the tablet and the punches and dies so that the tablet compression and ejection processes are smooth. Disintegrants (e.g. starch or cellulose) are used to promote wetting and swelling of the tablet so that it breaks up in the gastrointestinal tract; this is necessary to ensure dissolution of the API. Superdisintegrants are sometimes used to greatly speed up the disintegration of the tablet. Additional ingredients may also be added such as coloring agents, flavoring agents and coating agents. Formulations are designed using small quantities in a laboratory machine called a Powder Compaction Simulator. This can prove the manufacturing process and provide information.

Advantages[1]:

- They are unit dosage forms and they offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- They are the lightest and most compact oral dosage forms.
- They are in general the easiest and cheapest to package.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They may provide the greatest ease of swallowing with the least tendency for "hang-up" above the stomach especially when coated provided the tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products such as enteric or delayed release products.
- They are better suited to large scale production than other unit oral forms.

Disadvantages:

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.

- Drugs with poor wetting, dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features may be difficult to impossible to formulate and manufacture as a tablet that will still provide adequate full drug bioavailability.

- Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression or the tablets may require coating. In such cases, the tablets may offer the best and lowest cost approach.

Types of tablets[1]:

The main reason behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patients perspective and utilize an approach that is unlikely to add complexity during regulatory approval process. To perceive each dosage form, tablets here are classified by their route of administration and by the type of drug the delivery system represent within that route.

Oral tablets for ingestion:

- Standard compressed tablets
- Multiple compressed tablets
    - Compression coated tablets
    - Layered tablets
    - Inlay tablets
- Modified release tablets
- Delayed action tablets
- Targeted action tablets
    - Floating tablets
    - Colon targeting tablets

- Chewable tablets
- Dispersible tablets

Tablets used in the oral cavity

- Lozenges and troches
- Sublingual tablets
- Buccal tablets
- Dental cones
- Mouth dissolving tablets

Tablets administered by other routes:

- Vaginal tablets
- Implants

Tablets used for prepare solution:

- Effervescent tablets
- Hypodermic tablets
- Soluble tablets

METHODS INVOLVED IN FORMULATION OF TABLETS[5]:

- Direct compression
- Dry granulation
- Wet granulation

Direct compression:

This method is used when a group of ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be changed. This is not very frequent because many tablets have active pharmaceutical ingredients which will not allow

for the direct compression due to their concentration or the excipients used in formulation are not conducive to direct compression.

Granulation is the process of collecting the particles together by creating bonds between them. There are several different methods of granulation. The most popular, which is used by over 70% of formulation in tablet manufacture is wet granulation.

Advantages of Direct Compression:

1. Cost Effectiveness
2. Stability.
3. Faster Dissolution
4. Less wears & tears of punches
5. Simplified Validation

Limitations of direct compression

1. Segregation
2. Cost
3. Low dilution potential
4. Re-workability
5. Lubricant sensitivity
6. Variation in functionality

Dry granulation:

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is recompressed and the resulting tablet or slug are milled to yield the granules. The other method is to precompress the powder with pressure rolls using a machine such as Chilsonator.

Roller compaction

The compaction of powder by means of pressure roll can also be accomplished by a machine called chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which

contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules.

Use: Use in the production of directly compressible excipients, the compaction of drugs and drug formulations, the granulation of inorganic materials, the granulation of dry herbal material and the production of immediate/sustained release formulations.

Processing steps:

Weighing of raw material, screening, mixing, and compression to slugs-milling-mixing-compression to finished tablets.

Advantages:

The main advantage of dry granulation or slugging is that it uses less equipments and space. It eliminate the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

i) For moisture sensitive material.

ii) For heat sensitive material.

iii) For improved disintegration since powder particles are not bonded together by a binder.

Disadvantages:

i) It requires a specialized heavy duty tablet press to form slug.

ii) It does not permit uniform colour distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.

iii) The process tends to create more dust than wet granulation, increasing the potential for contamination.

Wet granulation:

The most broadly used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves the wet massing of the powder blend with a granulating liquid, wet sizing and drying.

Important steps involved in the wet granulation:

i) Mixing of the drug(s) and excipients.

ii) Preparation of binder solution.

iii) Mixing of binder solution with powder mixture to form wet mass.

iv) Drying of moist granules.

v) Mixing of screened granules with disintegrant, glidant, and lubricant.

Advantages

(a) Permits mechanical handling of powders without loss of mix quality.

(b) Improves the flow of powders by increasing particle size and sphericity.

(c) Increases and improves the uniformity of powder density.

(d) Improves cohesion during and after compaction.

(e) Reduces air entrapment.

(f) Reduces the level of dust and cross-contamination.

(g) Allows for the addition of a liquid phase to powders (wet process only).

(h) Makes hydrophobic surfaces hydrophilic.

Limitation of wet granulation:

i) The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.

ii) Loss of material during various stages of processing.

iii) Stability may be major concern for moisture sensitive or thermolabile drugs.

iv) Multiple processing steps add complexity and make validation and control difficult.

v) An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

Chewable tablets[1]:

Chewable tablets are intended to be chewed in the mouth prior to swallowing and are not intended to be swallowed intact. The purpose of the chewable tablet is to provide unit dosage form of medication which can be easily administered to infants and children or to the elderly, who may have difficulty in swallowing a tablet intact.

Chewable dosage forms, such as soft pills, tablets, gums and most recently chewy squares have long been part of the pharmacist armamentarium.

Advantages[6]:

- Better bioavailability through bypassing disintegration.
- Patient convenience through the elimination of the need for water for swallowing.
- Possible use as a substitute for liquid dosage forms where rapid onset of action is needed.
- Improve patient acceptance (especially in pediatrics).
- Better stability.

Techniques used in the formulation of chewable tablets[6]:

- Coating by wet granulation
- Microencapsulation
- Solid dispersion
- Adsorbate formation technique
- Ion exchange
- Spray congealing and spray coating
- Formation of different salts or derivatives
- Use of amino acids and protein hydrolysates
- Inclusion complexes
- Molecular complexes

COATING BY WET GRANULATION:

This process may be described as one which agglomerates drug particles through a combination of adhesion and cohesion using a wetting agent and binder. This process is primarily intended to impart flow ability and compressibility to imputable substances, under certain conditions it may be useful in the application of coatings to drug particles in order to mask or reduce the bitter taste .Taste improvement by coating is attractive in its simplicity, this method only suffix for mildly to moderately and pleasant tasting drugs .

MICROENCAPSULATION:

Microencapsulation is a method of coating drug particles or liquid droplets with edible polymeric materials there by masking the taste and forming relatively free flowing microcapsules of 5 to 5000µm.This process essentially consists of three steps

1. Formation of three immiscible phases.

2. Depositing the liquid polymer coating by sorption around the core material under controlled physical mixing of the three phases.

3. Rigidizing the coating, by thermal cross linking or desolvation techniques, to form a rigid microcapsule.

The resultant coated granules not only mask the taste of the drug but also minimize any physical and chemical incompatibility between ingredients.

SOLID DISPERSION:

Bad tasting drugs can be prevented from stimulating the taste buds by adsorption onto substrates capable of keeping the drugs adsorbed while in the mouth but releasing them eventually in the stomach or gastrointestinal tract. The adsorbent is commercially available in the form of micronized powder with the drug content of 10% w/w.

ADSORBATE FORMATION TECHNIQUE:

Solvent method

The formation of an adsorbate involves the drug in a solvent, mixing the solution with the substrate and evaporating the solvent leaving the drug molecules adsorbed up on the substrate.

Melting method

The drug or drugs and a carrier are melted together by heating the melted mixture. It is then cooled and rapidly solidified in a ice bath with vigorous stirring .The product is then pulverized and sized.

ION EXCHANGE:

The reversible interchange of ions between a solid and a liquid phase in which there is no permanent change in the structure of solid .The solid is the ion exchanger material while the ion could be a drug ion exchange materials provide a means for binding drugs on to an insoluble polymeric matrix and can effectively mask the problems of taste and odour, in drugs to be formulated in to chewable tablets.

SPRAY CONGEALING AND SPRAY COATING:

The process of spray congealing involves cooling of melted substances in the form of fine particles during their travel in a spray nozzle to the distant vicinity of a spray chamber held at a temperature below their melting point .The application is best exemplified by the taste masking of the thiamine mononitrate, riboflavin, pyridoxine hydrochloride and niacinamide by fatty acids.

FORMATION OF DIFFERENT SALTS OR DERIVATIVES:

This approach is to modify the chemical composition of the drug substance itself , so as to render it less soluble in saliva and thereby less stimulating for the taste buds , or to obtain a tasteless or less bitter form.

USE OF AMINO ACIDS AND PROTEIN HYDROLYSATES:

By combining amino acids, their salts, or a mixture of two, it is possible to substantially reduce the bitter taste of penicillin. Some of the preferred amino acids are sarcosine, alanine, glycine, glutamic acid.

INCLUSION COMPLEXES

In inclusion complex formation, the drug molecule (guest molecule) fits into the cavity of a complexing agent (host molecule) forming a stable complex. The complex is capable of masking the bitter taste of the drug by both decreasing the amount of drug particles exposed to the taste buds and decreasing the drug solubility on ingestion.

MOLECULAR COMPLEXES:

It involves a drug and a complexing organic molecule and, like inclusion complexes, can be used in the masking of the bitter taste or odour of drugs by forming complexes.

Role of disintegrants in the manufacturing of chewable tablets[7]:

Disintegrants are substances commonly included in tablet formulations and in some hard shell capsule preparations to benefit penetration and dispersion of the matrix of the dosage form in dissolution fluids. An oral solid dosage form should admirably disperse into the primary particles from which it was prepared. Disintegrants are the agents added to tablet (and some encapsulated) formulations to promote the breakup of the tablet (and capsule "slugs') into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance.

Mechanism of disintegrants:

There are four major mechanisms for tablets disintegration as follows

- Swelling:

The most widely recognised general mechanism of action for tablet disintegration is swelling. Tablets with high porosity and lack of adequate swelling force show poor disintegration. On the other hand, tablet with low porosity exert sufficient swelling force. It is worthy to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration slows down.

- Porosity and capillary action(Wicking):

Disintegration by capillary action is always the first step. When we add the tablet into a suitable aqueous medium, the medium penetrates into the tablet and replaces the air absorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet banks on hydrophilicity of the drug/excipient and on tabletting conditions. For these types of disintegrants sustainance of porous structure and low interfacial tension towards water is mandatory which helps in disintegration by creating a hydrophilic network around the drug particles.

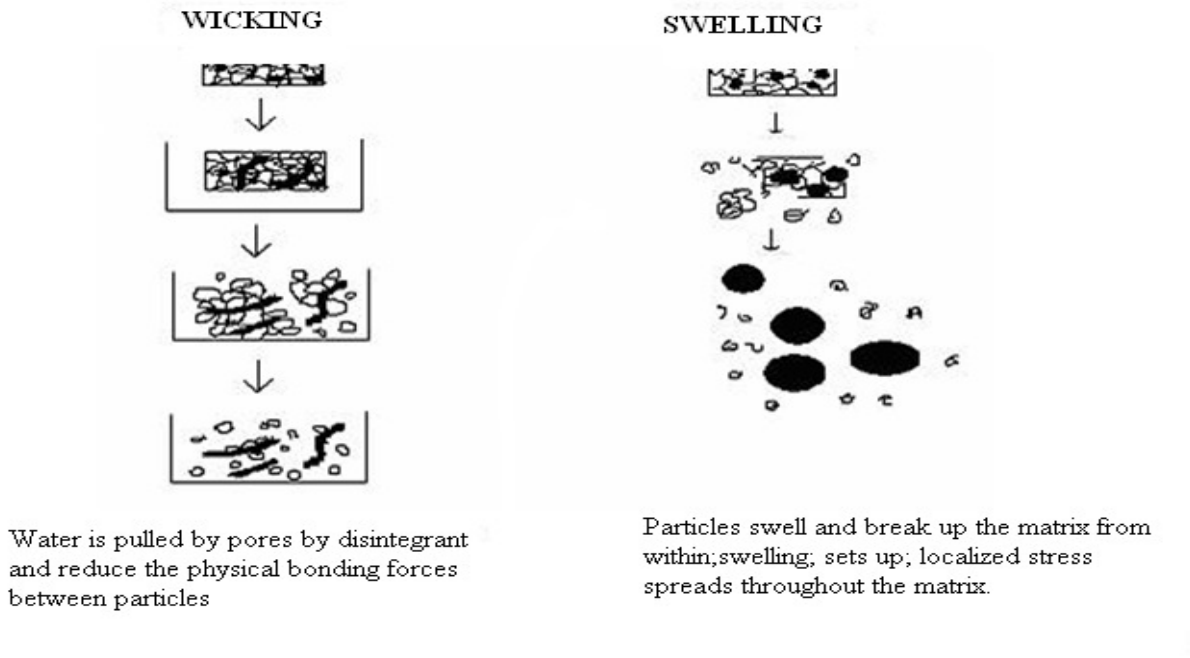


Fig No 1: Mechanism of disintegrants by swelling and wicking

- Due to disintegrating particles repulsive forces:

Another mechanism of disintegration attempts to elucidate the swelling of tablet made with 'nonswellable' disintegrants. Guyot-Hermann has adduced a particle repulsion theory based

on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles make the basis for disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

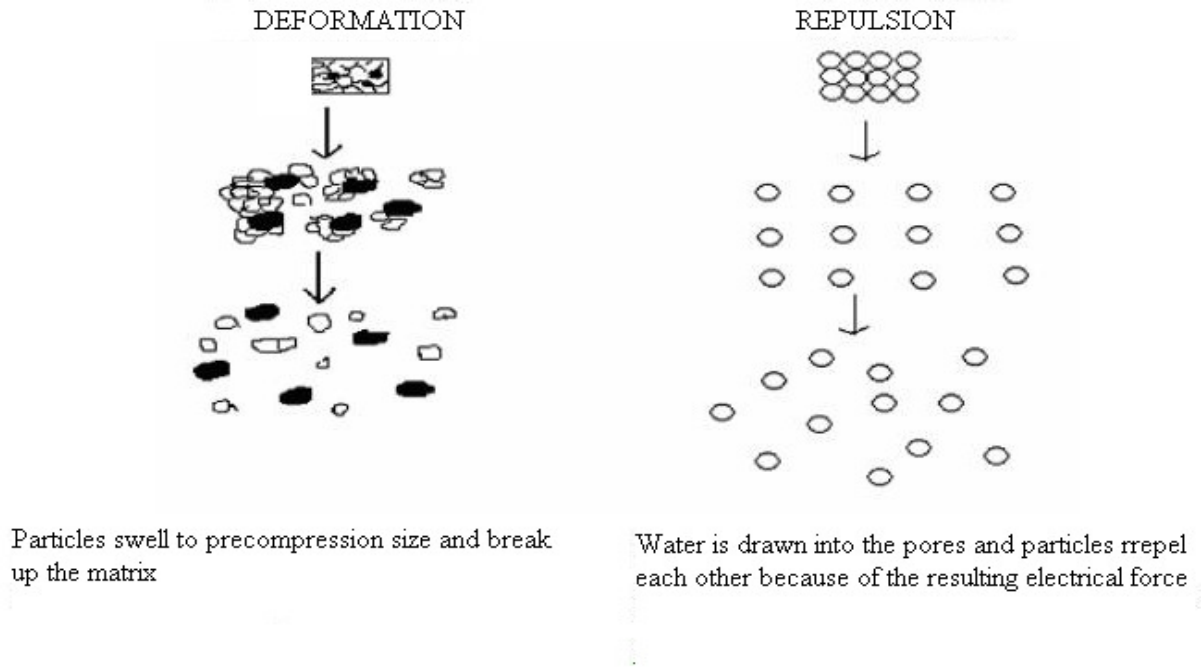


Fig No 2: Mechanism of disintegrants by deformation and repulsion

- Due to deformation:

During tablet compression, disintegrating particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally the swelling capacity of starch was increased when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet.

Method of addition of disintegrants[8]:

The ideal disintegrant should have the following characteristics:

- Poor solubility
- Poor gel formation
- Good hydration capacity
- Good molding and flow properties
- No tendency to form complexes with the drugs

Disintegrants are essentially added to tablet granulation for making the compressed tablet to break or disintegrate when placed in aqueous environment. Disintegrating agents can be added to tablets by two methods:

- Internal addition(Intragranular)

- External addition (Extra granular)
- Partly Internal and External

In extragranular method, the disintegrant is added to the sized granules with mixing prior to compression. In intragranular method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules. When these methods are employed, part of disintegrant can be added internally and part externally. This technique provides immediate disruption of the tablet into previously compressed granules while the disintegrating agent within the granules causes further erosion of the granules to the original powder particles. This two step method usually produces better and complete disintegration than the regular method of adding the disintegrant to the granulation surface only.

Factors effecting action of disintegrants:

- Percentage of disintegrants present in the tablets
- Types of substances present in the tablets
- Combination of disintegrants
- Presence of surfactants
- Hardness of the tablets.
- Nature of drug substances
- Mixing and screening

Because of the increased demands for improved dissolution requirements, there are currently, a new generation of "Superdisintegrants". These novel substances are more effective at lower concentrations with greater disintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants facilitate improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. They are widely used in wet granulation and direct compression applications.

Table No 1: Classification of superdisintegrants[9]

Structural type (NF name)	**Description**	**Trade name (manufacturer)**
Modified starches (sodium starch glycolate, NF)	Sodium carboxymethyl starch; the carboxymethyl groups induces	Explotab® (Edward Mendell Co.), Primojel® (Generichem Corp.),

	hydrophilicity and cross linking reduces solubility	Tablo® (Blanver, Brazil)
Modified cellulose (Croscarmellose,NF)	Sodium carboxy methyl cellulose which has been cross-linked to render the material insoluble.	AcDiSol® (FMC Corp.), Nymcel ZSX® (Nyma, Nertherlands), Primellose® (Avebe, Netherlands) Solutab® (Blanver,Brazil)
Cross-linked poly-vinylpyrrolidone (Crospovidone,NF)	Cross-linked polyvinylpyrrolidone; the high molecular weight and cross-linking render the material insoluble in water.	Crospovidone M® (BASF Corp.), Kollidon CL® (BASE Corp.), Polyplasdone XL (ISP Corp.)

Three major types of compounds have been developed which swell to many times their original size when placed in water while providing minimal viscosity effects.

1. Modified starches – Sodium Carboxymethyl (Chemically treated Potato Starch) starch i.e. Sodium Glycolate (Explotab, Primogel)
Mechanism of action: Rapid and extensive swelling with minimum gelling.
Effective Concentration: 4-6%. Above 8% disintegration times may actually increase due to gelling and its subsequent viscosity providing effects.

2. Cross-linked polyvinylpyrrolidone - water insoluble and strongly hydrophilic i.e., Crospovidone (Polyplasdone XL, Kollidon CL)
Mechanism of action: swelling, water wicking and possibly some deformation recovery.
Effective Concentration: 2-4%

3. Modified Cellulose – cross-linked form of Sodium carboxymethyl cellulose internally. i.e., Ac-Di-Sol (Accelerates Dissolution), Nymcel
Mechanism of action: wicking because of fibrous structure, swelling with minimum gelling.
Effective Concentration: 1-3% (Direct Compression), 2-4% (Wet Granulation)

Advantages:
- Effective in lower concentration than starch.
- Less effect on compressibility and flow ability.

- More effective intragranularly.

Disadvantages:

- More hygroscopic (may be problem with moisture sensitive drugs)
- Some are anionic and may cause slight in vitro binding with cationic drugs (not a problem in vivo)

Excipients used in the formulation of chewable tablets[6,10]:

Excipients are inert (unreactive) substances used as diluents or vehicles for a drug. In the pharmaceutical industry it is a catch all term which various sub-groups comprising diluents or fillers, binders or adhesives, disintegrants, lubricants, glidants, flavors, colors and sweeteners. All of these must meet certain criteria as follows:

- They must be physiologically inert
- They must be acceptable to regulatory agencies
- They must be physiologically and chemically stable.
- They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
- They must not interface with the bioavailability of the drug.
- They must be commercially available in the form and purity commensurate to pharmaceutical standards.
- Cost must be relatively inexpensive.
- They must conform to all regulatory requirements.

To assure that no excipient interferences with the utilization of the drug, the formulator must carefully and critically evaluate combinations of the drug with each of the contemplated excipients and must have certain compliance of each ingredient with existing standards and regulations.

The screening of drug-excipient and excipient-excipient interactions should be carried out routinely in pre formulation studies.

Table No 2: List of excipients used in the formulation of chewable tablets

Excipients	Functions	Examples
Diluents	Diluents are fillers used to make required bulk of tablet	Lactose, Microcrystalline cellulose, Mannitol etc.
Binders	Binders are used to impart cohesive qualities to powdered materials.	Gelatin, Glucose, Acacia, ethyl cellulose, hydroxypropyl methyl cellulose etc.
Superdisintegrants	They facilitate tablet breaking when it comes in contact with water in oral cavity/GIT	Croscarmellose sodium, Crospovidone, Sodium starch glycolate, Starch etc.
Lubricants	These are added to prevent adhesion of tablet material to surface of dies and punches reduces inter particulate friction.	Magnesium sterate, Talc, Paraffin, sodium lauryl sodium, etc.
Glidants	These are added to improve flow characteristics of powder mixture. Glidant minimize the friction between particles.	Colloidal Silicon dioxide (Aerosil), Corn starch, Talc etc.
Sweeteners	These are added to produce a palatable dosage form.	Sucrose, Saccharin, Aspartame, etc.
Flavours	These are added to improve taste of dosage form	Peppermint, Vanilla, Orange, Cinnamon, Mango, Cherry etc.
Colours	These are added for better appearance of dosage form	Sunset yellow (Supra),Ferric oxide.

Packaging of chewable tablets:

Some of the chewable tablets are stable during storage, e.g. for 18 months or even 24 months in conventional packaging and these type of dosage forms are stored in HDPE bottles and blister packs.

Some examples of chewable tablets [6]:

- Acetaminophen chewable tablets
- Common antacid chewable tablets
- Children's buffered aspirin chewable tablets.
- Chewable multivitamin tablets.
- Vitamin **C** chewable tablets.

ASTHMA [11, 12]:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.

Airflow obstruction (excessive airway narrowing) in asthma result in the contraction of the airway smooth muscle and swelling of the airway wall due to:

- Smooth muscle hypertrophy and hyperplasia
- Inflammatory cell infiltration
- Oedema
- Goblet cell and mucous gland hyperplasia
- Mucus hypersecretion
- Protein deposition including collagen
- Epithelial desquamation.

This inflammatory process can cause the permanent changes in the airways. Long-term changes include:

- Increased smooth muscle.
- Increase in bronchial blood vessels.
- Thickening of collagen layers.
- Loss of normal distensibility of the airway.

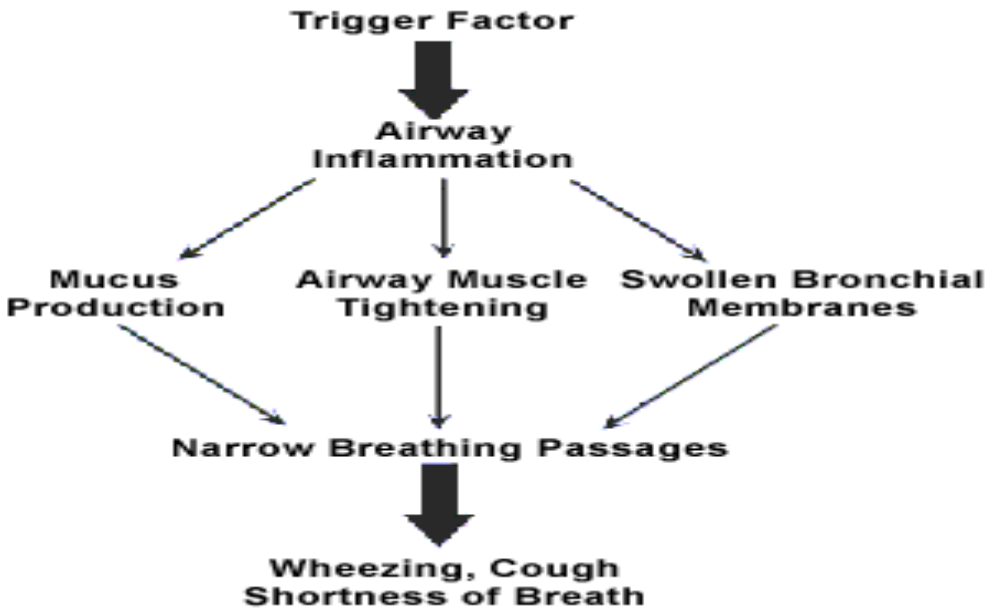


Fig No 3: Air flow obstruction in asthma

Types of Asthma[13]

- Extrinsic asthma
- Intrinsic asthma
- Mixed asthma
- Cough variant asthma:
- Nocturnal asthma
- Gastro-esophageal asthma

Extrinsic asthma:

Extrinsic asthma is also known as atopic asthma or allergic asthma. It is the most common form of asthma in all age group. It usually affects young age group.

People with allergic asthma and their family members frequently have other allergy related problems such as fever, skin rashes, hives, eczema, and rhinitis.

Intrinsic asthma:

The intrinsic asthma is not related with the allergies. In fact it is caused by inhalation of certain chemical such as cigarette smoke, fumes of motor vehicles and factories, strong odours, intake of certain medicines like aspirin; chest infections, stress, laughter, exercise, cold air, food preservatives like azinomoto or a myriad of other factors. Antibodies are not produced by the body and the cause of developing intrinsic asthma may be the irritation of the nerves or muscle in the airway**.**

Mixed asthma:

It is mixture of allergic asthma and intrinsic asthma. These people react to some allergies but their asthma is also triggered by other things also. For example symptoms are aggravated in an asthmatic while facing the chest infection

Cough variant asthma:

Cough may be the sole manifestation of asthma or a distressing symptom. Although chronic cough can be a sign of many health problems, it may be the principal or only manifestation of asthma, especially in young children.

Nocturnal asthma:

Nocturnal asthma is defined as an overnight fall of more than 20% in the FEV1 or PEFR. This night time propensity is due to a number of reasons:

- Exposure to dust mite, animal dander.
- Gastro-esophageal reflux.
- Post nasal drip.
- Decreased cortisol level.
- Increased parasympathetic activity.
- Increased level of histamine.
- Increased sensitivity to histamine.
- The effect of medicines may wear off.

- Early morning fall in circulating adrenaline.
- Overnight changes in vagal tone.

Gastro-esophageal asthma:

Asthma may be caused or worsened by to gastro-esophageal reflux. The symptoms of GERD are common in both children and adults who have asthma. Medical management of GERD includes:

- Avoiding heavy meals, fried food, caffeine, and alcohol.
- Avoiding food and drink within 3 hours of retiring.
- Elevating the head of the bed on 6- to 8-inch blocks.
- Using appropriate pharmacologic therapy.

Exercise Induced Asthma:

Exercise induced asthma only refers to asthma that occurs only with exercise. Before exercise pulmonary functions tends to be normal, but within 5 to 10 minutes of exercise they tend to fall. Pulmonary functions comes back to normal after rest but some times tend to remain low for a longer time.

DRUGS USED IN ASTHMA[14, 15]:

Basic pharmacology of agents used in treatment of asthma

The drugs most used for management of asthma are adrenoceptor agonist or sympathomemetic agents (used as relievers or bronchodilators) and inhaled corticosteroids (used as controllers or anti-inflammatory agent)

SYMPATHOMIMETIC AGENTS:

Sympathomemetic agents relax airway smooth muscles and inhibit release of bronchoconstricting mediators from mast cells. They may also inhibit microvascular leakage and increase mucociliary transport by increasing ciliary activity. Sympathomimetic agents are Epinephrine, Ephedrine, Isoproterenol and Albuterol as they increase the rate and force of cardiac contraction.

BETA2 SELECTIVE DRUGS:

The β_{2-} selective aderenoceptor agonist drugs are the most widely used sympathomimetic for the treatment of asthma. They are effective after inhaled or oral administration and have a long duration of action. Some of the drugs are Albuterol, Terbutaline, Metaproterenol and Pirbuterol.

A new generation of long lasting β_2 selective agonist include Salmeterol and Formoterol.

METHYLAXANTHINE DRUGS:

The three important methylxanthines are Theophyline, Theobromine and Caffeine. Theophylline is most effective bronchodilator and relieves airflow obstruction in acute asthma and reduces the severity of symptoms.

CORTICOSTEROIDS:

They have been used to treat asthma by their broad anti-inflammatory cytokenins. They reduce bronchial reactivity and reduce the frequency of asthma exacerbation.

Examples-Beclomethasone, Buderonide, Fluticasone, Mometasone and Triamcinolone.

LEUKOTRIENE PATHWAY INHIBITORS:

Leukotriene results from the action of 5-lipoxygenase on arachidonic acid and are synthesized by a variety of inflammatory cells in the airways including eosinophils, mast cells, macrophages and basophils. Leukotriene $B_4(LTB_4)$ is a potent neutrophil chemo attractant. Examples-Zileuton, Ziafirlukast and Montelukast

The principal advantage is that they are taken orally. Some patients-especially children comply poorly with inhalation.

LITERATURE REVIEW

- **Janugade B.U** et.al.,[16] designed an oral press-coated tablet was prepared by using direct compression and wet granulation methods to achieve the predetermined lag time. The tablet contained Montelukast sodium in the inner core was formulated with an outer barrier layer by different compositions of hydrophobic polymer ethylcellulose and hydrophilic polymer low-substituted hydroxypropylcellulose in different concentrations. From lag time it was observed that lag time decreases with increasing concentration of low-substituted hydroxypropylcellulose.The tablets coated by wet granulation method gives less lag time as compared to dry mixing blend method.

- **Ajay** et.al.,[17] formulated a mouth dissolving tablets of Montelukast sodium by direct compression method using superdisintegrants such as croscarmellose sodium and crospovidone. The compatibility of the drug in the formulations was confirmed by IR studies. The formulations were subjected to precompression and postcompression parameters and the results were found to be within acceptable limits. The formulated tablets disintegrated in less than 26.33sec fulfilling the official requirements for dispersible tablets. The rapid drug release was observed in the formulations containing croscarmellose sodium. Finally, it can be concluded that mouth dissolving tablets of Montelukast sodium can be prepared by direct compression method using croscarmellose sodium as superdisintegrant.

- **Surender et.al**.,[18] Formulated and evaluated colonic pulsatile release matrix tablets of Montelukast sodium. It was formulated by wet granulation method using different combinations of HPMC K4M and K15M with varying amount of croscarmellose sodium, formulation was evaluated for *in vitro* tests such as hardness, friability, weight variation, disintegration and dissolution. The formulation was evaluated for drug release mechanism by applying Zero, First, Higuchi and Peppas kinetic models and selection was based on that of linearity. Dissolution data revealed that formulations having HPMC K4M : K15M in ratio of 20: 0 along with croscarmellose sodium at a level of 2.4% given a release rate of more than 85% in 12h of duration. Drug release data fits well to zero order kinetics and mechanism of drug release was found to be combination of swelling and erosion.

- **Ajay Patil** et.al.,[19] developed fast dissolving films of Montelukast sodium by using microcrystalline cellulose as superdisintegrant and crospovidine as plasticizer. Result showed that formulation F2 and F5 with 4% crospovidine and 10% microcrystalline cellulose gives a better dissolution profile at the end of 30 minutes.

- **N.G Raghavendra** et.al.,[20] performed a study to improve the improve the bioavailability and efficacy by designing tablets-filled-capsule system. System comprise of different doses of immediate release tablets (IRT) and sustained release tablets (SRT) contained in a HPMC capsule. The drug-loaded core tablets were produced by wet granulation technique using alcoholic solution of PVP K-30 as a binder. All the pre and post-compression parameter were evaluated. From this, study it was concluded that, tablets-filled-capsule systems containing Montelukast sodium showed both sustained release as well as immediate release may improve the bioavailability and efficacy.

- **Ahmed B.Eldin** et.al.,[21] developed and evaluated a simple, sensitive and accurate stability indicating analytical method for Montelukast. The chromatogram was performed with the mobile phase containing a mixture of acetonitrile and 0.01M potassium dihydrogen phosphate. Validation was done for linearity, accuracy and precision and showed that method is useful for routine quality control analysis and stability testing.

- **Khan** et.al.,[22] evaluated the process for preparing a chewable tablet of loratidine comprising a micronized form of an active ingredient, by combining the active ingredient with excipients by geometric dilution to form a final mixture and applying direct compression at least a portion of the final mixture to form at least one tablet.

- **Shaik** et.al.,[23] assessed the efficacy of Mebendazole in treatment of worm infestations in both humans and animals. The chewable tablets of Mebendazole were prepared by using excipients as lactose or mannitol along with sodium starch glycolate in concentration ratios.

From the disintegration studies, it was observed that the formulation containing lactose shows less disintegration time than formulation containing mannitol.

- **Rao N.G** et.al.,[24] formulated the buccal patches Montelukast sodium used in treatment of chronic asthma attacks. The buccal patches were prepared by using hydrophilic and hydrophobic polymers. The evaluation were characterized for number of parameters like physical appearance and surface texture, weight uniformity, thickness, folding endurance, swelling index, surface pH, drug content uniformity, *in vitro* residence time, bursting strength, drug–excipients interaction study, and *in vitro* drug release study.*In-vitro* dissolution was studied and was observed that patches followed zero-order and mechanism was diffusion rate limited and founded drug release in the range of 68.83 - 92.22 % in 8 hrs.

- **Swati Jagdale** et.al.,[25] evaluated chewable tablet of levamisole which is used in the treatment of worm infestations. As an anthelmintic, it probably works by targeting the nematode nicotinergics acetylcholine receptor. The chewable tablets of levamisole were prepared by using lactose or mannitol along with sodium starch glycolate in concentration ratios especially for paediatric use. Sodium saccharin and vanilla were used as sweetening agent and flavouring agent respectively. It was observed that the formulation containing lactose shows less disintegration time than formulation containing mannitol.

- **Kathiresan K** et.al.,[26] formulated and evaluated 5 batches of loratadine chewable tablets. Loratadine, which is histamine H1 receptor antagonist used in the treatment of allergic rhinitis and urticaria. Results showed that thickness, weight variation, friability, hardness, and content uniformity of all 5 formulations were within the acceptance limits. But in the *in-vitro* dissolution study, formulations 1, 2, and 5 demonstrated better cumulative drug release than formulations 3 and 4. However, cumulative drug release of formulation 5 was comparable with innovator than formulations 1 and 2. Hence the study concludes that loratadine chewable tablet formulated using avicel CE 15 and starch paste showed better characteristics of chewable tablets.

- **Bharat** et.al**.,**[27] performed a prospective study of Albendazole which is a benzimidazole derivative with broad spectrum anthelmenthic activity and excellent tolerability. Orally it is rapidly absorbed and metabolized to sulfoxide and sulfone, which may be responsible for its anthelmenthic action. Albendazole chewable tablets (400 mg) were prepared by three methods *viz.* non aqueous granulation, aqueous granulation and direct compression. Tablet prepared by these three methods were evaluated by the different parameters such as Average weight, Hardness, Carr's index, Tapped density, Friability, Disintegration, Water content, *In vitro* dissolution *etc.* All the parameters were found within the specifications. The study on the dissolution profile revealed that the product by 'Direct Compression**'** had faster dissolution rate while compared to remaining batches and marketed product and the assay values were within the limits of 90% to 110%.

AIM AND OBJECTIVE OF WORK

Aim:

Montelukast sodium is used in the treatment of asthma. The usual dose is 4mg, 5mg and 10mg to children and adults. Now the present aim is to formulation and development of chewable tablets using different concentration of disintegrants to improve the onset of action and the bioavailability in the treatment of asthma.

Objectives:

I. To find out suitable concentration of disintegrant for the formulation of Montelukast sodium chewable tablets.
II. To evaluate the pre-compression parameters such as bulk density, tap density compressibility index and hausner's ratio.
III. To evaluate the post compression parameters such as physical appearance, hardness, thickness, average weight, friability, disintegration time and assay.
IV. To perform *In vitro* dissolution studies and compare with that of innovator product.
V. To perform the stability study under the accelerated condition.
VI. To mask the bitter taste of Montelukast sodium by converting into a chewable tablets.

PLAN OF WORK

The study was planned to carry out as follows,

1. Preparation of mixed blend of drug and excipients by using superdisintegrant Croscarmellose sodium in the concentration of 1% to 4% by direct compression and wet granulation technique.
2. Checking Drug and Excipient compatibility by FTIR Studies
3. Pre compression studies, like

    a. Angle of repose

    b. Bulk density

    c. Tapped density

    d. Compressibility index

    e. Hausner's ratio

4. Preparation of chewable tablets.

5. Evaluation of prepared tablets

    a. Appearance
    b. Weight variation test
    c. Hardness
    d. Thickness
    e. Friability
    f. Disintegration
    g. Water content
    h. Assay
    i. Dissolution
    j. Stability studies

DRUG PROFILE

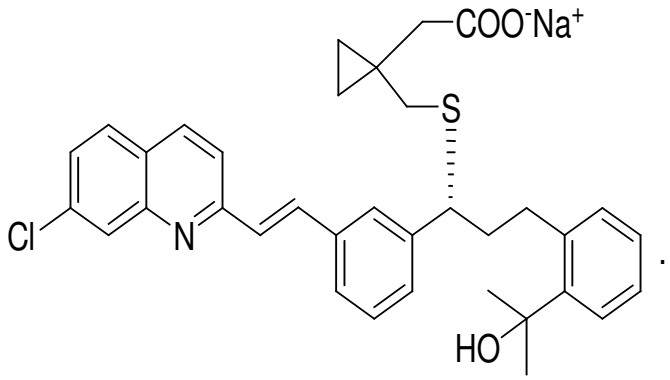
MONTELUKAST SODIUM [28]

Category : Antiasthmatic

Molecular formula : $C_{35}H_{35}ClNNaO_3S$

Molecular weight : 608.17

Structural formula :



Chemical name: 2-[1-[1(R)-[3-[2(E)-(7-Chloroquinolin- 2-yl) vinyl] phenyl]-3-[2-hydroxy-1- methylethyl) phenyl] propylsulfanylmethyl] cyclopropyl] acetic acid sodium salt

Description: Off white to pale yellow coloured powder.

Solubility: Soluble in water, methanol and ethanol and practically insoluble in acetonitrile.

Mechanism of action[29]:

The cysteinyl leukotrienes (LTC4, LTD4, LTE4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 (CysLT1) receptor is found in the human airway (including airway smooth muscle cells and airway

macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction. Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity.

Pharmacodynamics:

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatics. Doses as low as 5 mg cause substantial blockage of LTD4-induced bronchoconstriction. In a placebo-controlled, crossover study (n=12), montelukast inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75% and 57%, respectively.

Pharmacokinetics:

Absorption:

Montelukast is rapidly absorbed following oral administration. Mean peak plasma concentration (C_{max}) is achieved 3 hours (T_{max}) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal.

Distribution:

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of Montelukast averages 8 – 11 liters.

Metabolism:

Montelukast is extensively metabolized in liver by cytochrome P450 isoenzyme CYP3A4, CYP2A6 and CYP2C9

Excretion:

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

Dosage and administration:

- The dosage for adults and adolescents 15 years of age and older is one 10-mg tablet.
- The dosage for pediatric patients 6 to 14 years of age is one 5-mg chewable tablet.
- The dosage for pediatric patients 2 to 5 years of age is one 4-mg chewable tablet or one packet of 4-mg oral granules.
- The dosage for pediatric patients 6 to 23 months of age is one packet of 4-mg oral granules.

Overdosage:

Abdominal pain, headache, psychomotor hyperactivity, somnolence, thirst, vomiting.

CONTRAINDICATIONS

- Hypersensitivity to any component of this product
- Status asthmaticus

Drug Interactions

- **Gemfibrozil**: Montelukast plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions. Monitor the clinical response and adjust the montelukast dose as needed.
- **Prednisone**: Adverse effects of prednisone (Eg. edema) may be increased. Monitor the clinical response. If an interaction is suspected, consider discontinuing one or both agents.
- **Strong CYP2C9 and CYP3A4 inducers (Eg, phenobarbital, rifampin)**: May decrease montelukast levels. Monitor the clinical response and adjust the montelukast dose as needed.

Side effects:

Montelukast has manageable side effects such as given below:

- Severe allergic reactions such as rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue; headache (18% to 20%) and dizziness (2%).
- **Gastrointestinal:** Gastrointestinal side effects have included abdominal pain, dyspepsia, or infectious gastroenteritis in up to 3% of patients. Diarrhea has been associated with the use of higher than recommended doses
- **Respiratory:** Respiratory system side effects have included influenza (4%), cough (3%), and nasal congestion (2%). In some studies, upper respiratory tract infection

(28%) and worsened asthma (4% to 11%) were associated with the use of this drug. However, many patients with asthma have some or all of these symptoms, and a causal relationship has not been proven. Rhinorrhea, sinusitis, otitis, influenza, epistaxis, and pneumonia have also been reported.

- **Ocular:** Ocular side effects have included conjunctivitis.
- **Other:** Other side effects have included isolated cases of Churg-Strauss syndrome, a rare systemic vasculitis associated with asthma.

PRECAUTIONS

- It is not a fast-acting asthma medication and cannot replace fast-acting rescue inhalers. Do not use montelukast to treat an asthma attack.
- Some reports were studied that who were taking an oral steroid may be able to decrease or stop this medication when starting montelukast.
- Chewable montelukast tablets contain phenylalanine. This is important information for people with phenylketonuria (PKU) is a rare condition in which a baby is born without the ability to properly break down an amino acid called phenylalanine.), who must limit their phenylalanine intake.
- In some it can cause liver damage. So care should be taken while taking the medication.
- Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or nonsteroidal anti-inflammatory agents while taking montelukast sodium drug.

Storage/Stability

- Store between 59° and 86°F. Protect from moisture and light.

Administration:

Give with or without food.

Table No 3: Route of administration

Route	Onset	Peak	Duration
P.O.	Unknown	3-4 hr	Unknown
P.O. (chewable)	Unknown	2-2.5 hr	Unknown
P.O. (granules)	Unknown	Unknown	Unknown

EXCIPIENT PROFILE

1.MICROCRYSTALLINE CELLULOSE[30]

Non-proprietary Names

BP: Microcrystalline cellulose

PhEur: Cellulose microcrystalline

Synonym: Cellulose gel, crystalline cellulose,E460, Emcocel, Fibrocel, Tablose, Vivacel.

Chemical Name : Cellulose

Empirical formula : $(C_6H_{10}O_5)_n$ where n ≈ 220

Molecular weight : 36000

Melting Point : 260-270°C

Particle size: (MCC pH102) = 100 µ m

Description: MCC is purified, partially depolymerized cellulose that occur as a white, odorless, crystalline powder composes of porous particle. It is commercially available in different particle size and moisture grades that have different properties and application.

Functional Category: Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrants.

Table No 4: Uses of Microcrystalline Cellulose

Use	**Concentration (%)**
Adsorbent	20-90
Antiadherent	5-20
Capsule binder/ diluents	20-90
Tablet disintegrant	5-15
Tablet binder/ diluents	20-90

Stability and Storage: It is stable though hygroscopic material. The bulk material should be stored in well closed container in a cool and dry place.

Incompatibility: It is incompatible with strong oxidizing agent.

2.MANNITOL[30]

Nonproprietary Name:

BP: Mannitol

JP: D-Mannitol

PhEur: Mannitolum

USP: Mannitol

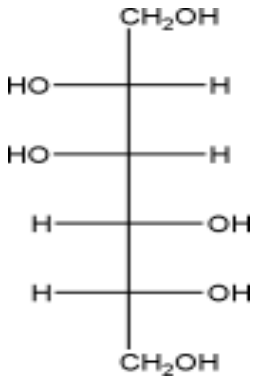
Synonyms: Cordycepic acid; E421; manna sugar; D-mannite; mannite; *Mannogem; Pearlitol*

Chemical Name : D-Mannitol

Empirical Formula : $C_6H_{14}O_6$

Molecular Weight : 182.17

Structural Formula:



Functional Category: Diluent, sweetening agent

Applications in Pharmaceutical Formulation or Technology:

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.

Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations.

Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.

Description:

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth.

3. CROSCARMELLOSE SODIUM[30]

Nonproprietary Names:

BP: Croscarmellose sodium

PhEur: Carmellosum natricum conexum

USPNF: Croscarmellose sodium

Synonyms : Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical Name : Cellulose, carboxymethyl ether, sodium salt, crosslinked

Functional Category : Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules.

In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should

be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Table No 5: Uses of croscarmellose sodium

Use Concentration	**(%)**
Disintegrant in capsules	10–25
Disintegrant in tablets	0.5–5.0

Description: Croscarmellose sodium occurs as an odorless, white or greyish white powder.

Stability and Storage Conditions: Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at

30^0C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities: The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury and zinc.

4.ASPARTAME[30]

Nonproprietary Names:

BP: Aspartame

Ph Eur: Aspartamum

USPNF: Aspartame

Synonyms: 3-Amino-N-(α-carboxyphenethyl) succinamic acid N- methyl ester; 3-Amino-N-(α- methoxycarbonyl phenethyl) succinamic acid; Aspartyl pheylamine methyl ester;

Chemical name **:** N-α-L-Aspartyl-L-phenylalanine 1-methyl ester.

Emperical formula **:** $C_{14}H_{18}N_2O_5$

Molecular weight **:** 294.31

Functional category **:** Sweetening agent

Applications in Pharmaceutical Technology:

Aspartame is used as an intense sweetening agent in beverage products, food products, table top sweeteners and in pharmaceutical preparations including tablets, powder mixes and vitamin preparations It enhances flavour systems and can be used to mask some

unpleasant taste characteristics; the approximate sweetening power is 180-200 times that of sucrose. Therapeutically, aspartame is used in the treatment of sickle cell anemia.

Description: Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

Solubility: Slightly soluble in ethanol (95%), sparingly soluble in water. At 20^0C the solubility is 1%w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperatures and at more acidic pH, e.g. at pH 2 and 20^0C solubility is 10%w/v.

5. MAGNESIUM STEARATE[30]

Nonproprietary names:

BP: Magnesium Stearate

JP: Magnesium Stearate

Ph Eur: Magnesii stearas

USPNF: Magnesium Stearate

Synonyms: Magnesium octadecananoate; Octadecanoic acid; Magnesium salt; Stearic acid, magnesium salt.

Chemical name: Octadecanoic acid magnesium salt

Emperical formula: $C_{36}H_{70}MgO_4$

Molecular weight: 591.34

Functional category: Tablet and capsule lubricant.

Applications in Pharmaceutical Technology: Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 and 5%w/w. It is also used in barrier creams.

Description: Magnesium stearate is a fine, white, precipitated or milled, Impalpable powder of low bulk density, having a faint odour or and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in warm benzene and warm ethanol (95%).

6. HYDROXY PROPYL CELLULOSE[30]

Nonproprietary Names

BP: Hydroxypropylcellulose

JP: Hydroxypropylcellulose

PhEur: Hydroxypropylcellulosum

USPNF: Hydroxypropyl cellulose

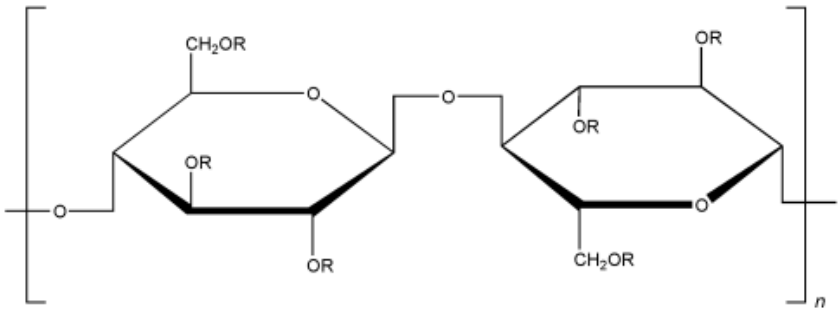
Synonyms: Cellulose, hydroxypropyl ether; E463; hyprolose; Klucel; Methocel; Nisso HPC; oxypropylated cellulose.

Chemical Name: Cellulose, 2-hydroxypropyl ether

Empirical Formula: $[CH_2CH(CH_3)O]_mH$

Molecular Weight: 50 000–1 250 000;

Structural Formula:



R is H or $[CH_2CH(CH_3)O]_mH$

Functional Category:

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations;

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating, and extended-release-matrix former. Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes. Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release. The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Aqueous solutions containing hydroxypropyl cellulose along with an amount of methyl cellulose or ethanolic solutions have been used. Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Description: Hydroxypropyl cellulose is a white to slightly yellow-coloured, odourless and tasteless powder.

Typical Properties:

Melting point*:*

Softens at 130°C; chars at 260–275°C.

Moisture content: Hydroxypropyl cellulose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air. Typical equilibrium moisture content values at 25°C are 4% w/w at 50% relative humidity and 12% w/w at 84% relative humidity

Solubility: Soluble 1 in 10 parts dichloromethane; 1 in 2.5 parts ethanol (95%); 1 in 2 parts methanol; 1 in 5 parts propan-2-ol; 1 in 5 parts propylene glycol and 1 in 2 parts water. Practically insoluble in aliphatic hydrocarbons; aromatic hydrocarbons; carbon tetrachloride; petroleum distillates; glycerin; and oils.

7. Ferric Oxide[31]

Synonyms

(a) Iron oxide black: black magnetic oxide; black oxide, black rouge; ethiopsiron; ferric ferrous oxide; ferrosoferric oxide;iron oxides(FeO); magnetite.
(b) Iron oxide red: anhydrous ferric oxide; anhydrous iron(III)oxide; diiron trioxide; hematite; red ferric oxide; Sicovit R30
(c) Iron oxide yellow monohydrate: hydrated ferric oxide; iron (III) oxide monohydrate, yellow ferric oxide; ferric hydroxide; iron hydrated; iron hydroxide; yellow iron oxide

Chemical Name: Iron oxides: Iron oxide black, Iron oxide red, Iron oxide yellow.

Empirical Formula and Molecular Weight:

(a) Fe_3O_4 : 231.54

(b) Fe_2O_3 : 159.70

(c) $Fe_2O_3.H_2O$: 177.70 (monohydrate); $FeHO_2$: 88.85(hydrate)

Density :

Iron oxide black (Fe_3O_4): $5.1\,g/cm^3$

Iron oxide red (Fe_2O_3): $5.2\,g/cm^3$

Iron oxide yellow ($Fe_2O_3.H_2O$): $4.1\,g/cm^3$

Description: Iron oxides occur as yellow, red, black, or brown powder. The color depends on the particle size and shape, and crystal structure.

Melting point : 1565^0C for iron oxide red (Fe_2O_3).

Solubility: Soluble in mineral acids; insoluble in water.

Stability and Storage Conditions: Iron oxides should be stored in well-closed containers in a cool, dry place.

Incompatibilities: Iron oxides have been reported to make hard gelatin capsules brittle at higher temperatures when the residual moisture is 11–12%. This factor affects the use of iron oxides for coloring hard gelatin capsules, and will limit the amount that can be incorporated into the gelatin material.

Applications in Pharmaceutical Formulation or Technology:

Iron oxides are widely used in cosmetics, foods, and pharmaceutical applications as colourants and UV absorbers. As inorganic colorants they are becoming of increasing importance as a result of the limitations affecting some synthetic organic dye stuffs. However, iron oxides also have restrictions in some countries on the quantities that may be consumed, and technically their use is restricted because of their limited color range and their abrasiveness.

MATERIALS AND METHODS

LIST OF EQUIPMENTS:

Table No 6: List of equipments

Equipment	**Manufacturer**
Electronic balance	Mettler-Toledo, USA
Bulk density apartments	Electro lab, Mumbai
Rapid Mixer Granulator (RMG)	Anchor Mark Pvt. Ltd.,
Tablet compression machine (single rotary 16 punches)	Cadmach machinery Co Pvt Ltd.,INDIA
Friability test apparatus	Electro lab, Mumbai
Tablet dissolution apparatus	Electro lab, Mumbai
Disintegration apparatus	Electro lab, Mumbai
Blender	Erweka
Electronic Thickness	Mitutoyo,Japan
Hot air over	Eltek motors, Mumbai
High performance liquid chromatography (HPLC)	Shimadzu Scientific Instruments
Sieves	Jayanth test sieves, Mumbai
Hardness tester	Dr.Schleuniger pharmatron, USA
Fluidized bed dryer	Anchor Mark Pvt. Ltd.,
Stability chamber	Thermo labs

LIST OF CHEMCALS

Table No 7: List of chemicals

Ingredients	Manufacturer	Supplier
Montelukast sodium	M/s Aptuit Laurus Private Ltd., Hyderabad	M/s Aptuit Laurus Private Ltd, Hyderabad
Mannitol	Colorcon, UK	Ansul Agencies, Mumbai
Croscarmellose sodium	Maple Biotech Pvt. Ltd.	Maple Biotech Pvt. Ltd
MCC PH 101	FMC Biopolymer, USA	Signet Chemical Corporation, Mumbai
MCC PH 102	FMC Biopolymer, USA	Signet Chemical Corporation, Mumbai
Hydroxypropyl cellulose	Merck limited, Mumbai	Vasco Scientifics Pvt. Ltd.,
Ferric oxide	ISP Technologies INC, USA	Signet Chemical Corporation Mumbai
Magnesium sterate	_	Ferro Chemical Corporation
Cherry flavor	Tridient pharmaceuticals Pvt.Ltd	Tridient pharmaceuticals Pvt.Ltd.

METHODS

PREFORMULATION STUDIES

Drug-excipient compatibility studies: [32]

The compatibility studies provide the scheme for the drugs combination with excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets.

Compatibility studies were carried out by mixing definite proportions of Montelukast sodium and Mannitol, Cellulose microcrystalline, Croscarmellose sodium, Hydroxypropyl cellulose, Magnesium sterate, Aspartame, Ferric oxide and Cherry flavor in the ratios of 1:1,1:2.5,1:3,1:5,1:10 and kept in glass vials, which are stored at 50^0C(3 weeks).

FTIR Spectroscopy:[33]

All the excipients used in the different formulations were mixed with the drug separately in equal

ratios and the samples of the final formula of the chewable tablet were analyzed through FTIR studies. FT-IR spectra (400-4400cm-1) were obtained on a Perkin-Elmer FT-IR spectrophotometer with a resolution of 4 cm-1. KBR pellets were prepared gently by mixing the 1mg sample with 100 mg potassium bromide. The characteristic peaks were recorded.

Pre-compression parameters:[32,34]

a) **Angle of repose:**

The internal angle between the surface of the pile of blend and the horizontal surface is known as the angle of repose.

Method:

The blend was passed through a funnel fixed to a burette stand at a height of 4 cm. A graph paper was placed below the funnel on the table. The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula:

$$\text{Angle of repose } (\theta) = \tan^{-1} (h/r)$$

Where,

h = Height of the pile

r = Radius of the pile

b) Bulk density:

The bulk density is used as a measure to describe packing materials of granules.

Method:

Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by transferring an accurately weighed amount (25 Gms) of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

$$\text{Bulk density} = W/V_0 \text{ g/ml}$$

Where,

W = Mass of the blend

V_0 = Untapped volume

c) Tapped density:

Method

It was measured by transferring a known quantity (25 Gms) of blend into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus was set for 500, 750 and taps. The tapped density was determined as the ratio of mass of the blend to the tapped volume.

Tapped density = W/V_f g/ml

Where,

W = Mass of the blend

V_f = Tapped volume

d) Compressibility index:

It is the property of a powder to be compressed.

Method:

It is measured by tapped density apparatus for 500, 750 and 1250 taps for which the difference should be not more than 2%. Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula.

% Compressibility = [(Tapped density – Bulk density) / Tapped density] X 100

e) Hausner's ratio:

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powder is called Hausner's ratio.

Hausner ratio= Tapped density / Bulk density

Table No 8: Flow properties and corresponding Angle of repose, compressibility index and Hausner's ratio:

S.NO Flow prop erties	Angle of response (θ)	Compressibility Index (%)	Hausner's ratio	
1	Excellent	25-30	<10	1.00-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Passable	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37 1.46-1.59	
7	Very very poor	>66	>38	>1.6

Post compression parameters:

f) Physical Appearances:

The tablets were inspected for smoothness, absence of cracks, chips an other undesirable characteristics.If they are coloured, it includes examination for mottling and other evidence of non uniform colour distribution except her they are intentionally.

g) Weight variation test:[35]

20 tablets were randomly selected from each batch and their average weight was calculated using digital balance. Individual weight of each tablet was also calculate using the same and compared with the average weight.

Table No 9: Weight variation requirements:

Average weight of tablet (mg)	%Difference
130 or less	10%
From 130 to 324	7.5%
>324	5%

h) Thickness:

Thickness was determined for 20 pre- weighted tablets of each batch using a digital vernier scale and the average thickness was determined in mm. The thickness of the tablets mostly related to the tablet hardness and can be used as an initial control parameter.

a) Thickness:

Thickness was determined for 20 pre- weighted tablets of each batch using a digital vernier scale and the average thickness was determined in mm. The thickness of the tablets mostly related to the tablet hardness and can be used as an initial control parameter.

b) Percentage Friability:

The friability test gives an indication of tablets ability to rest chipping and abrasion on handling during packaging and shipping. Usually for conventional tablets friability value of 1.0% or less is desirable. If the tablet weight is >_ 650 mg 10 tablets were taken and initial weight was noted. The tablets were rotate in the Roche friabilator for 100 revolutions at 25rpm. The tablets were dedusted and reweighed.

The tablets that loose less than 1% weight were considered to be compliant.

The percentage friability is expressed as the loss o weight and is calculated by the formula:

% Friability = (A-B/A) * 100

Where,

A= Initial weight of tablets

B= Final weight of tablets after 100 revolutions

c) Disintegration time:[35]

Disintegration time is the time taken by a tablet to break up into granules of specified size (or smaller), under carefully specified test conditions. The disintegration test is carried out in an apparatus containing basket rack assembly with six glass tubes of 7.75 cm length and 2.15mm in diameter the bottom of which consists of 10 mesh sieve. The basket is raised and lowered 28-32 times per minute in the medium of 900 ml which is maintained at $\pm 2^0$C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the sieve (# 10) was considered as the disintegration time of the tablet.

d) Water content (By KF Method)

Instrument: Karl Fischer Titrator:

35 ml of mixture of methanol was transferred to the titration vessel and titrated with Karl Fischer reagent to the electrometric point, to consume any moisture that may be present (disregard the volume consumed, since it does not enter into the calculation). Powder from 5 tablets was used, ground to a fine powder in an atmosphere of temperature and relative humidity known no to influence the results. 300-500 mg of the powder was accurately weighed and transferred into the titration vessel, mixed and titrated with Karl Fischer reagent to the electrometric end point; finally the water content of the specimen in mg was calculated.

e) Preparation of standard curve for Montelukast sodium:

Standard graph for Montelukast Sodium:

Accurately weigh and transfer about 55 mg of Montelukast working standard into a 100 ml clean, dry volumetric flask, add about 70 ml of methanol and sonicate to dissolve. Dilute to volume with methanol and mix.

f) Dissolution study (By HPLC method):

The dissolution test calibrates the rate of release of the drug from the dosage form *in vitro*; it is usually expressed as extent of dissolution (% drug content) occuring after certain time under specified conditions. For effective absorption of oral solid dosage form, simple disintegration of the dosage form is not adequate and the dissolution of the drug to the surrounding medium plays a vital role. Though dissolution is not a predictor of therapeutic efficacy it can be looked upon a tool which can provide valuable information about biological availability of drug and batch to batch consistency. Dissolution is considered as one of the most important quality control tests performed for pharmaceutical dosage form.

Instrument: A High Performance Liquid Chromatograph System equipped with Photodiode array detector and data handling system (Shimadzu scientific instruments).

Dissolution parameters:

Medium : Purified water with 0.5% SLS

Volume : 900ml

Temperature : $37^0C \pm 0.5^0C$

Apparatus : USP Type-II (Paddle)

Rotating speed: 50RPM

Time point : 30 minutes

Chromatographic conditions:

Column : Hypersil BDS $C_{8,}$ 5µ (100 mm x 4.6mm)

Pump mode : Isocratic

Flow rate : 2.0 ml/min

Detection : UV, 345 nm

Injection Volume : 20 µL

Column temperature : 40°C

Run time : 10 minutes

Procedure:

The in vitro dissolution study was done in the USP dissolution test apparatus, type II (paddle). One tablet was placed in each of the six dissolution flasks containing 900 ml of dissolution medium, previously maintained at 37^0C $\pm$ 0.5^0C. After completion of each specified time interval, 10ml of the solution was withdrawn from zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1 cm from vessel wall and filtered through 0.45µm membrane filter. The samples were collected at specified time intervals and diluted to required volume with dissolution medium and inject the solution into chromatograms and record the chromatograms.

g) Assay (By HPLC method):

Instrument: A High Performance Liquid Chromatograph System equipped with Photodiode array detector and data handling system (Shimadzu scientific instruments).

Chemicals and reagents:

Potassium Dihydrogen Orthophosphate : AR grade
Orthophosphoric acid (≈88 % w/w) : AR grade
Acetonitrile : HPLC grade
Methanol : HPLC grade
Water : Milli-Q grade.

Chromatographic conditions:

Column	: Hypersil BDS C_8, 5µ (100 mm × 4.6 mm) or equivalent
Pump mode	: Isocratic
Flow rate	: 2.0 ml/min.
Detection	: UV, 345 nm.
Column temperature	: 40°C
Injection volume	: 20 µL

Preparation of buffer:

Dissolve 6.8 g of potassium dihydrogen orthophosphate in 1000 ml of water. Adjust the pH to 3.5 ± 0.05 with orthophosphoric acid. Filter through 0.45 µm nylon membrane filter.

Preparation of Mobile phase:

Prepare a degassed mixture of buffer and acetonitrile in the ratio of 45:55 v/v.

Diluent preparation:

Use mobile phase as a diluent.

Standard preparation:

Accurately weigh and transfer about 50 mg of Montelukast working standard into a 100 ml clean, dry volumetric flask, add about 70 ml of methanol and sonicate at room temperature to dissolve. Dilute to volume with methanol and mix. Further dilute 5 ml of this solution to 50 ml with diluent and mix. Filter through 0.45 µm nylon membrane filter.

Sample preparation:

Weigh and transfer 10 tablets into a 250 ml clean, dry volumetric flask. Add about 170 ml of diluent and sonicate for 30 minutes with intermittent shaking at room temperature. Dilute to volume with diluent and mix. Centrifuge the solution at 10000 RPM for 10 minutes. Transfer 5 ml of supernatant solution into a 20 ml clean, dry volumetric flask, dilute to volume with diluent and mix. Filter through 0.45 µm nylon membrane filter.

Procedure:

Inject the sample solution, into the chromatograph. Record the chromatograms and measure the peak areas.

Calculation:

Calculate the amount of Montelukast by using the following formula:

$$\text{Content of Montelukast (mg / tablet)} = \frac{A_T}{A_S} \times \frac{D_S}{D_T} \times \frac{P}{100}$$

$$\% \text{ Labeled amount} = \frac{\text{Content of Montelukast (mg/tablet)}}{\text{Label claim, in mg}} \times 100$$

Where,

A_T = Average area count of Montelukast peak in the chromatogram of sample solution

A_S = Average area count of five replicate injections for Montelukast peaks in the chromatograms of standard solution, as obtained under system suitability

D_S = Dilution factor of standard solution (weight ÷ dilution)

D_T = Dilution factor of sample solution (weight ÷ dilution)

P = Percent potency of Montelukast working standard used (as is basis)

W = Theoretical weight of the blend, in mg.

SIMILARITY FACTOR AND DISSIMILARITY FACTOR CALCULATION[36]

The similarity factor (f2) was defined by CDER, FDA, and EMEA as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference release profiles".

Dissimilarity (f1) describes the relative error between two dissolution profiles. It approximates the percent error between the curves.

$$f1 = \{ [\sum_{t=1}^{n} |R_t - T_t|] / [\sum_{t=1}^{n} R_t] \} . 100$$

$$f2 = 50. \log \{ [1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100$$

The similarity factor f2 and its significance is shown in the following table

Table No 10.

Similarity factor F2 and its significance

S. No.	Similarity factor (F2)	Significance
1.	<50	Test and reference profiles are dissimilar.
2.	50 -100	Test and reference profiles are similar.
3.	100	Test and reference profiles are identical.
4.	>100	The equation yields a negative value.

ACCELERATED STABILITY STUDY OF OPTIMIZED FORMULATION: [37]

Stability of a pharmaceutical preparation can be defined as the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life.

The purpose of the stability testing is to provide an evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

ICH specifications for stability study:

- Long term testing: 25^0C ± 2^0C and 60%± 5% RH for 12 months.
- Accelerated testing: 40^0C ± 2^0C and 75%± 5% RH for 6 months.

Procedure:

In the present study, stability studies were carried out at 40 ^{0}C and 75% RH for a specific time period up to 60 days for optimized formulations. For stability study, the tablets were sealed in aluminum packaging coated inside with polyethylene. These sample containers were placed in desiccator's maintained at 75% RH.

Evaluation of samples:

The samples were analyzed for the following parameters:

I. Physical evaluation:

   Appearance: The samples were checked for any change in color at every month.

II. Chemical evaluation:

   Drug content: The samples were checked for drug content.

Drug release: The samples were subjected to drug release studies.

EXPERIMENTAL INVESTIGATION

Table No 11: Innovator product details:

Name of the product	Singulair junior
Manufacturer name	Merck Sharp &Dohme Limited, Germany
Description	Pink, round, debossedwith code`MSD275' on one side and `SINGULAIR' on the other side.
Package	PVC/aluminium blister pack

Table No 12: Physical parameters of innovator product:

Parameters	**5mg**
Thickness(mm)	4.42
Hardness(kg/cm^2)	2.8
Length(mm)	9.59
Width(mm)	9.66
Disintegration time (sec)	27

Table No 13: Dissolution profile of innovator product (SINGULAIR JUNIOR)

Time(min)	**Drug Release percentage**
10	90
15	95
20	95
30	96

FORMULATION DEVELOPMENT OF MONTELUKAST SODIUM CHEWABLE TABLETS

Table No 14: Ingredients

S.NO	INGREDIENTS
1	MONTELUKAST SODIUM
2	MANNITOL
3	CELLOSE,MICROCRYSTALLINE
4	HYDROXYPROPYL CELLOSE
5	CROSCARMELLOSE SODIUM
6	FERRIC OXIDE
7	ASPARTAME
8	ARTIFICAL CHERRY FLAVOUR
9	MAGNESIUM STERATE
10	PURIFIED WATER

Direct compression method

Table No 15: Formula for F1

S NO	INGREDIENTS	QUANTITY(mg)
1	Montelukast sodium	5.19
2	Mannitol	199.31
3	Cellulose,microcrystalline(PH102)	75.00
4	Croscarmellose sodium	9.00
5	Hydroxypropyl cellulose	6.00
6	Ferric oxide	0.60
7	Aspartame	1.50
8	Artificial cherry flavour	0.40
9	Magnesium sterate	3.00

Procedure

1. Montelukast Sodium, Hydroxypropyl cellulose and one fourth of Cellulose, Microcrystalline (PH 102) were sifted through # 40 mesh.
2. Red Ferric oxide was sifted through # 100 mesh and added to materials of step 1.
3. The materials of step 2 were re-sifted through #40 mesh.
4. Remaining Cellulose, Microcrystalline (PH 102) was sifted through #40 mesh and added to materials of step 3.
5. The materials of step 4 were re-sifted through # 40 mesh.
6. Mannitol, Croscarmellose Sodium, Ferric oxide, Aspartame, Artificial cherry flavour was sifted through # 40 mesh.
7. The materials of step 6 were re-sifted through # 40 mesh.
8. Magnesium stearate was sifted through # 60 mesh.
9. The above blend of step 7 was lubricated with Magnesium Stearate.
10. The lubricated blend was compressed into tablets.

WET GRANULATION METHOD:

Table No 16: Formula for F2 to F8

S.NO	INGREDIENTS	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)
INTRAGRANULAR EXCIPIENTS								
1	Montelukast sodium	5.19	5.19	5.19	5.19	5.19	5.19	5.19
2	Mannitol	201.61	201.61	200.11	198.61	199.61	199.61	196.61
3	Cellulose Microcrystalline	59.00	57.50	57.50	59.50	57.00	55.50	59.00
4	Croscarmellose sodium	1.50	2.25	3.00	3.75	4.50	5.25	6.00
5	Ferric oxide	0.30	0.30	0.30	0.30	0.30	0.30	0.30
GRANULATING FLUID								
6	Hydroxypropyl cellulose	6.00	6.00	6.00	6.00	6.00	6.00	6.00
7	Purified water	Q.S	Q.S	.Q.S	Q.S	Q.S	Q.S	Q.S
EXTRAGRANULATING EXCIPIENTS								
8	Cellulose,microcrystalline	20.00	20.00	20.00	20.00	20.00	20.00	20.00
9	Croscarmellose sodium	1.50	2.25	3.00	3.75	4.50	5.25	6.00
10	Aspartame	1.50	1.50	1.50	1.50	1.50	1.50	1.50
11	Cherry flavour	0.40	0.40	0.40	0.40	0.40	0.40	0.40
12	Magnesium sterate	3.00	3.00	3.00	3.00	3.00	3.00	3.00
	Total	300	300	300	300	300	300	300

Procedure:

1. Intragranular materials i.e. Montelukast Sodium, 40% of Mannitol were passed through #40mesh.

2. Ferric oxide was passed through #80 mesh and was added to step 1.
3. The materials of step 2 were resifted through # 40 mesh.
4. Equal quantities of step 3 and remaining 60% mannitol were co-sifted through # 40 mesh.
5. Cellulose, Microcrystalline (PH 101) was sifted and resifted through # 40 mesh.
6. The above material was mixed with step 4 in rapid mixing granulator.
7. The binder solution was prepared by dispersing Hydroxypropyl cellulose in sufficient quantity of purified water.
8. The dry mix of step-6 was granulated using binder solution of step-7 to get wet mass of desired consistency.
9. The wet mass was dried in fluid bed dryer at 60ºC ± 5ºC.
10. Dried granules were milled in Co-mill using 1.13mm screen at medium fast speed.
11. Extragranular excipients i.e. Cellulose, Microcrystalline, Croscarmellose Sodium were sifted through #40mesh.
12. Artificial cherry flavour and Aspartame was passed through # 60 mesh.
13. The above materials of step 11 & step 12 were blended with the dried granules of step 10.
14. Magnesium stearate was passed through #60mesh.
15. The above blend was lubricated with Magnesium stearate of step 14.
16. Then finally the lubricated blend was compressed into Tablets.

RESULTS AND DISCUSSION

Table No 17: DRUG–EXCIPIENTS COMPATIBILITY STUDIES

S.NO	Ingredients	Ratio	Description	
			Initial	**50^0C(3 weeks)**
1	Montelukast Sodium	-	Off white to pale yellow colour powder.	NCC
2	Montelukast Sodium +Mannitol	1:10	white colour powder	NCC
3	Montelukast sodium+cellulose microcrystalline (PH 101)	1:10	White to off white colour powder	NCC
4	Montelukast sodium+cellulose microcrystalline (PH 102)	1:5	White to off white colour powder	NCC
5	Montelukast sodium+croscarmellulose sodium	1:2.5	White to off white colour powder	NCC
6	Montelukast sodium+hydroxypropyl cellulose	1:3	Off white to cream colour powder	NCC
7	Montelukast sodium+aspartame	1:1	White to off white colour powder	NCC
8	Montelukast sodium+cherry flavour	1:1	Off white to cream colour powder	NCC
9	Montelukast sodium+ferric oxide	1:1	light pink color powder	NCC
10	Montelukast sodium sodium + magnesium sterate	1:1	White powder	NCC

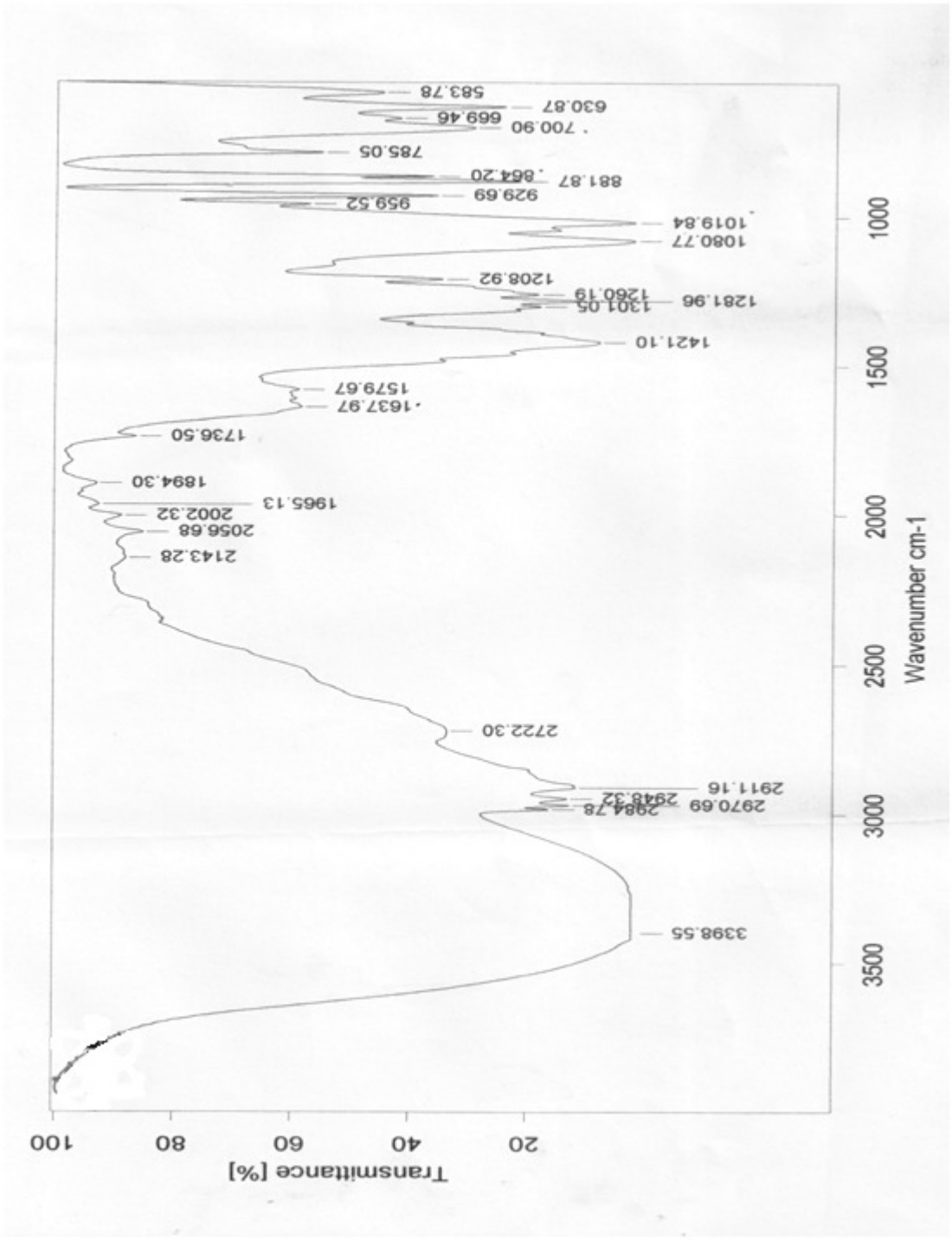


Fig No 5: FTIR Spectra of Montelukast sodium final formulation

Discussion:

The drug and excipient compatability studies were performed by means of physical mixture of drug and excipients in different ratios (1:1,1:1,1:2.5,1:3,1:5,1:10) at 50^0C for one month and no characteristic change were observed. The compatability was studied with IR and peaks indicate that there is no interaction with excipients and so drug is compatable with the formulation components.

Table No 18: Pre-compression parameters for formulation:

Formula	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio
F1	42.8±0.03	0.466±0.04 0.626±0.01	25.55±0.51	1.34±0.98	
F2	37.23±0.02	0.581±0.06	0.735±0.04	20.95±0.40	1.26±0.22
F3	32.21±0.01	0.588±0.05	0.757±0.02	22.32±0.36	1.28±0.12
F4	29.24±0.01	0.595±0.03	0.769±0.02	22.62±0.22	1.29±0.23
F5	24.70±0.03	0.602±0.04	0.781±0.08	22.91±0.21	1.29±15
F6	20.8±0.08	0.617±0.04	0.806±0.03	23.44±0.19	1.30±0.12
F7	22.71±0.01	0.641±0.04	0.833±0.02	23.04±0.17	1.29±0.29
F8	39.69±0.02	0.649±0.03	0.862±0.03	23.70±0.51	1.32±0.98

Mean±SD, (n=3)

Discussion:

The blends was analysed for the parameters such as angle of repose, bulk density, tapped density, compressibility index, hausner`s ratio, and were found to be within limits. F1 formulation done by direct compression was found to be sticking to the punches of the tablet press, so it was not taken further studies. So F2 TO F8 formulation wet granulation was taken for further studies.

Table No 19: Post compression parameters

Formula	Avg. weight(mg)	Thickness(mm)	Hardness(kg/cm^2)	Friability (%)
F2	301±0.12	4.31±0.0005	3.2±0.17	0.99
F3	297.0±0.23	4.29±0.0012	3.0±0.12	0.39
F4	297.4±0.12	4.28±0.0031	3.4±0.14	0.28
F5	298.0±0.01	4.25±0.0034	3.2±0.02	0.20
F6	301.5±0.25	4.26±0.0051	3.2±0.15	0.16
F7	302.2±0.14	4.25±0.0059	3.1±0.10	0.15
F8	301.4±0.28	4.28±0.0032	3.1±0.01	0.19

Mean±SD,(n=3)

Discussion:

Tablets hardness of each formulation was analysed and found to be good in the range of 3 to 4.5 kg/cm^2. So they were taken for further studies.

Tablets thickness was almost uniform in all formulation and was found to be in the range of 4.25mm to 4.60mm.

The total weight of each formulation was not maintained constant, but the weight variation was within limits of ±5%.

Friability were found to be less than 1% and considered to be satisfactory in the range of 0.15% to 0.99%.

Table no 20: Post compression parameters

Formula	Disintegration time (sec)	Water content (w/w)	Assay(%)
F2	65±2	1.92±0.05	101.4±0.03
F3	62±3	1.90±0.09	98.7±0.01
F4	50±2	1.90±0.01	98.0±0.1
F5	42±4	1.84±0.17	100.5±0.18
F6	36±1	1.73±0.05	99.2±0.01
F7	38±3	1.71±0.5	99.3±0.03
F8	38±1	1.75±0.02	99.0±0.5

Mean±SD,(n=3)

Discussion:

The prepared tablets were checked for disintegration time, water content and assay and all the tests formulations were passed. The assay ranges were found to be 99 to 102%.

The disintegration time was within 1-1.5 minutes. The water content done by Karl fisher method was also within range of 1.70 to 1.95%w/w.

In Vitro Dissolution Study

TABLE NO 21: Data for Standard Curve of Montelukast sodium

S. No.	Conc. (µg/ml)	Response
1	10	581819
2	20	1159645
3	30	1739469
4	40	2298302
5	50	2904228

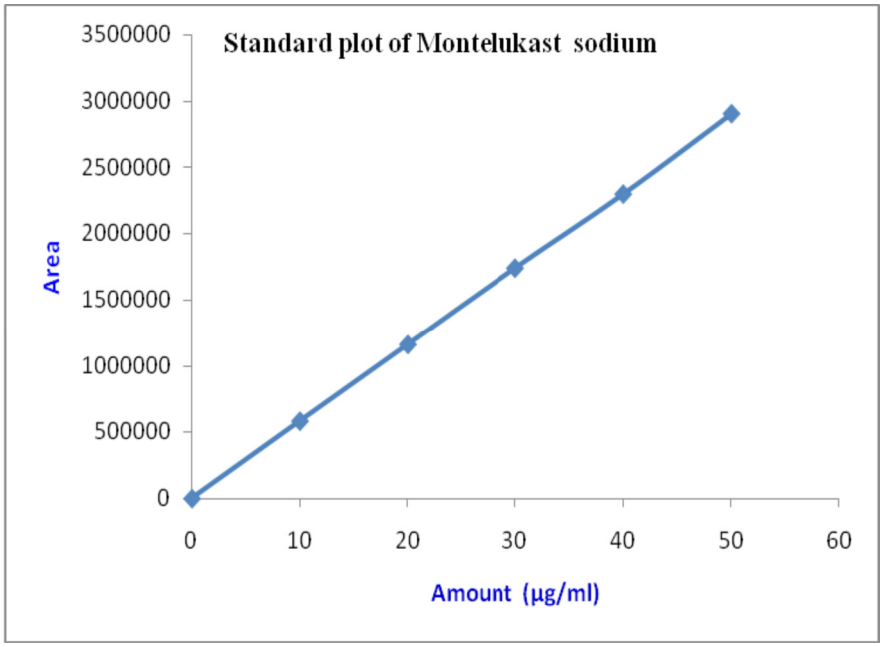


Fig. No 6: HPLC Chromatogram for Montelukast sodium in methanol

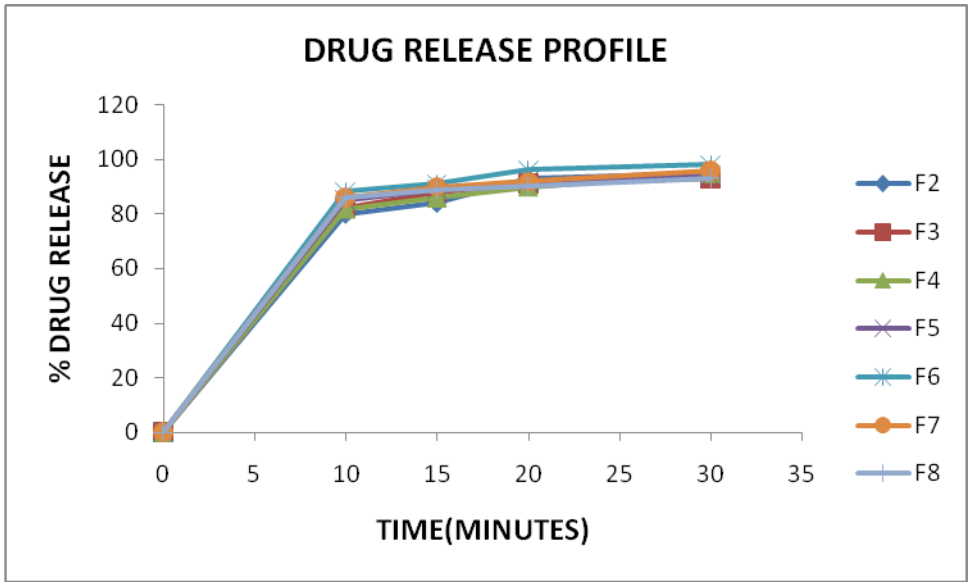
Table No 22: In Vitro dissolution data by HPLC analysis for Montelukast sodium.

Peak Name	Rt(min)	Area (μV^2 sec)	Theoretical plates	Tailing Factor	Resolution
Montelukast sodium	5.501	581819	2640	1.3	-

Table No 23: In Vitro release profiles study of different formulation:

Sampling time (minutes)	Drug release profile (% drug release)						
	F2	F3	F4	F5	F6	F7	F8
10	80±0.90	82±0.52	82±0.43	85±0.24	88±0.23	86±0.28	86±0.90
15	84±0.82	88±0.85	86±0.56	89±0.51	91±0.29	90±0.35	89±0.82
20	93±0.28	91±0.68	90±0.76	92±0.73	96±0.40	92±0.73	90±0.54
30	95±0.58	93±0.72	95±0.23	94±0.04	98±0.20	96±0.26	93±0.29

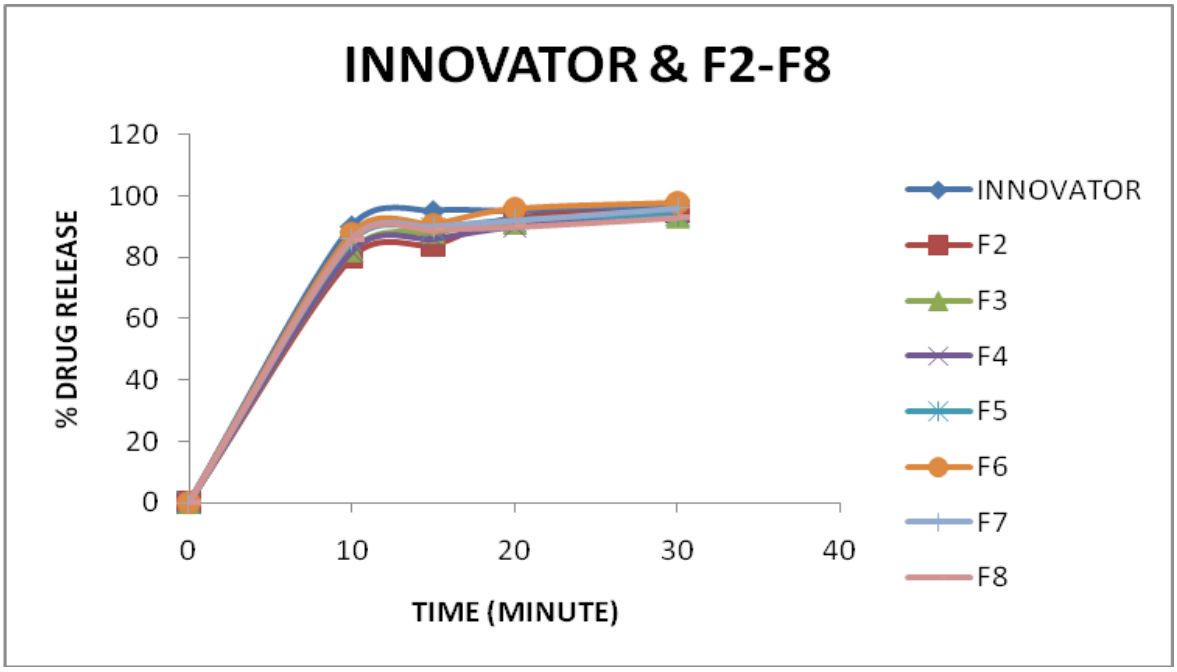
Fig No 7: Comparative *In Vitro* drug release profile of Formulation F2 to F8



Discussion:

In Vitro drug release profiles for all formulations were carried out by using purified water with 0.5% SLS as dissolution medium for 30 minutes. From the results obtained it was observed that the formulation F6 with3% concentration of croscarmellose sodium (superdisintegrant) shows better release rate with 98% within 30 minutes. So, the formulation F6 was found to give best release rate with 98% (Cumulative % drug release). So F6 formulation was taken for stability studies.

Fig No8: In Vitro drug release profile of formulation F2 –F8 and innovator product.



Stability data

Table No24 : Physical and chemical parameters of Montelukast sodium tablets (F6) after 1 month at 40ºC ± 2ºC/75 %RH ± 5 %RH(packing: blister pack)

Parameter	Initial	1 month
Description	Pink colour round shaped tablets	No change
Avg. weight(mg)	301.0	301.2
Hardness(kg/cm^2)	3.2	3.0
Thickness(mm)	4.26	4.29
Friability (%)	0.16	0.14
Water content(w/w)	1.73	1.63
Assay (%)	99.2	101.2

Table No 25: Dissolution profile of Montelukast sodium tablets (F6) after 1 month at 40ºC ± 2ºC/75 %RH ± 5 %RH(packing: blister pack)

Time interval (min)	Drug release percentage	
	Initial	Final
10	88	86±0.25
15	91	89±0.59
20	96	94±0.15
30	98	96±0.85

Table No 26: Physical and chemical parameters of Montelukast sodium tablets (F6) after 1 month at 40ºC ± 2ºC/75 %RH ± 5 %RH(packing: HDME BOTTLE)

Parameter	Initial	1 month
Description	Pink colour round shaped tablets	No change
Avg. weight(mg)	301.0	301.2
Hardness(kg/cm^2)	3.2	3.0
Thickness(mm)	4.26	4.29
Friability (%)	0.16	0.14

Water content(w/w)	1.73	1.63
Assay (%)	99.2	101.2

Table No 27: Dissolution profile of Montelukast sodium tablets (F6) after 1 month at 40ºC ± 2ºC/75 %RH ± 5 %RH(packing: HDME BOTTLE)

Time interval (min)	Drug release percentage	
	Initial	Final
10	88	86±0.84
15	91	88±0.51
20	96	93±0.63
30	98	96±0.19

Mean±SD, (n=3)

Discussion:

Form the above 1 month stability data there was no characteristic change in the formulation F6.

SUMMARY AND CONCLUSION

Montelukast sodium is a leukotriene receptor antagonist used in maintenance and treatment of asthma.

Montelukast sodium chewable tablets 300mg were formulated by using different concentration of superdisintegrant croscarmellose sodium in 1 to 4% concentration.

FT-IR study performed for the identification and compatibility study of drug and excipients and found that there was no characteristic change in the drug –excipients powder mixture. Hence, these excipients were selected for the formulation development. The Powder and blends were evaluated for tests such as bulk density, tapped density, compressibility index, hausner's ratio before being punched as tablets.

The development was started with direct compression method (F1). The blend was having poor flow property and was found to be sticking to the die walls of the compression machine resulting in weight variation of tablets. So it was not taken for further studies.

Formulations F2 to F8 were formulated using wet granulation technique where concentration of croscarmellose sodium (superdisintegrant) was gradually increased from 1% to 4%. In formulation F2 to F6 the drug release increased upto 98% at the end of 30 minutes and in the formulation F7 and F8 the drug release was decreased to 93% in 30 minutes. In limit concentration (1-3%) of croscarmellose sodium as superdisintegrant there was an increase in the release of the drug for F2 to F6 and after a limit concentration (3.5-4%) of superdisintegrant there was a decrease in drug release in F7 and F8.

The formulation F2 to F8 were compared with that of innovator for drug release and the final formulation F6 showed *In vitro* drug release (98%) which was found to be matching to that of innovator.

The optimized batch (F6) tablets were packed in HDPE container and Blister packs and are further studied for stability at 40^0C ± 2^0C/ 75% RH ± 5%RH for a period of one month. Tablets were evaluated for assay and *In vitro* dissolution, but there was no significant change during the study period.

CONCLUSION

It can be concluded that chewable tablets of Montelukast sodium can be prepared by wet granulation method using croscarmellose sodium as superdisintegrant. Chewable tablets of Montelukast sodium with 3% of croscarmellose sodium gave better drug release of 98% with minimum disintegration time with pleasant taste .This will improve patient compliance and increase in bioavailability.

SCOPE FOR FURTHER STUDIES:

- Long term stability studies can be performed to assure quality of Montelukast sodium chewable tablets 5mg.
- Clinical studies can be conducted for the approved batches.

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